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Lactobacilli versus antibiotics to prevent urinary tract infections: a randomized, double-blind, noninferiority trial in postmenopausal women

Beerepoot *et al.*, *Arch Intern Med* 2012; **172**: 704–712; doi:10.1001/archinternmed.2012.777

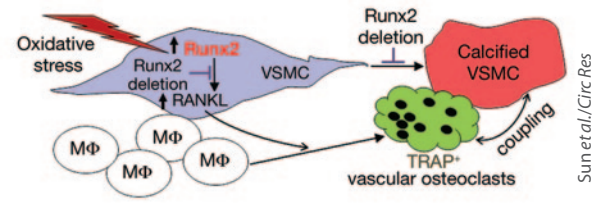
There is growing concern among family physicians and specialists alike about the development of resistant bacterial strains secondary to overuse of antibiotics. The development of these resistant strains is a particular concern in nephrology in the management of urinary tract infections (UTIs) in postmenopausal women, in whom some of the natural defense mechanisms are no longer in effect. Beerepoot *et al.* studied non-antibiotic therapy (lactobacilli treatment prophylaxis) compared with antibiotics for recurrent UTIs in postmenopausal women. Two hundred fifty-two postmenopausal women with recurrent UTIs were randomized in a double-blind noninferiority trial to receive 12 months of prophylaxis with 480 mg trimethoprim-sulfamethoxazole once daily or oral capsules containing lactobacillus twice daily. Primary end points were the mean number of symptomatic UTIs, the proportion of participants with at least one UTI during 12 months, the time to first UTI, and the development of antibiotic resistance by *Escherichia coli*. The authors reported that in comparison with the year prior to the trial, the mean number of UTIs was approximately 7 in both groups, whereas during the 12 months of the study the numbers were 2.9 for the antibiotic group and 3.3 for the yeast group. The between-treatment difference of 0.4 UTIs per year (95% confidence interval, –0.4 to 1.5) was outside the estimated noninferiority margin. At least one symptomatic UTI occurred in 69.3% and 79.1% of the trimethoprim-sulfamethoxazole and lactobacilli participants, respectively; median times to the first UTI were 6 and 3 months, respectively. After 1 month of trimethoprim-sulfamethoxazole prophylaxis, resistance to trimethoprim-sulfamethoxazole, trimethoprim, and amoxicillin had increased from 20% to 40% to 80% to 95% in *E. coli* from the feces and urine of asymptomatic women and among *E coli.* causing a UTI. In contrast, resistance was not increased during lactobacilli prophylaxis. The authors conclude that in postmenopausal women with recurrent UTIs, lactobacilli therapy did not meet the noninferiority criteria in the prevention of UTIs compared with trimethoprim-sulfamethoxazole.

Although this study was not able to demonstrate noninferiority to antibiotics, an important point to note is that the lactobacilli treatment did not increase antibiotic resistance, which suggests this therapy may be a suitable alternative to antibiotics, especially in patients in whom strain resistance has been previously demonstrated.

Daniel Cattran

Dependence of vascular calcification on vascular smooth muscle cell expression of Runx2

Sun *et al.*, *Circ Res* 2012; **111**: 543–552; doi:10.1161/CIRCRESAHA.112.267237



Model for the functional contribution of Runx2 to vascular calcification. Oxidative stress induces the expression of Runx2 in VSMCs, which directly promotes osteogenic differentiation and calcification of VSMCs *in vitro* and *in vivo*. In addition, increased Runx2 directly upregulates the expression of receptor activator of nuclear factor-κB ligand (RANKL) in VSMCs by binding to the *RANKL* promoter, which in turn promotes infiltration of macrophages and formation of vascular osteoclasts in the calcified atherosclerotic lesions. Abbreviations: MΦ, macrophage; TRAP, tartrate-resistant acid phosphatase.

Vascular calcification is a major risk factor for cardiovascular morbidity and mortality, particularly in patients with atherosclerosis, diabetes, and/or chronic kidney disease. Many factors contribute to the pathogenesis of arterial calcification, either positively as promoters or negatively as inhibitors. The osteogenic runt-related transcription factor 2 (Runx2, also known as Cbfa1), which is essential for osteoblast differentiation and chondrocyte maturation, appears to be one of the major promoters of vascular smooth muscle cell (VSMC) calcification, on the basis of previous experiments performed *in vitro*. Sun *et al.* now provide experimental evidence *in vivo* for the role of Runx2 in vascular calcification. They generated VSMC-specific Runx2-deficient mice in an apolipoprotein $E^{-/-}$ background, by breeding SM22α-Cre transgenic mice with Runx2 exon 8 floxed mice. Deletion of Runx2 exon 8 was verified by PCR analysis. The animals exhibited normal aortic gross anatomy and expression levels of VSMC-specific marker genes. Runx2 deficiency did not affect basal VSMC markers but inhibited oxidative stress-reduced expression of these markers. High-fat diet-induced vascular calcification *in vivo* was markedly inhibited in the Runx2-deficient mice compared with their control littermates. Runx2 deficiency inhibited the expression of receptor activator of nuclear factor-κB ligand (RANKL), and this was accompanied by decreased macrophage infiltration and formation of osteoclast-like cells in the calcified lesions. Coculture of VSMCs with bone marrow–derived macrophages demonstrated that the Runx2-deficient VSMCs failed to promote differentiation of macrophages into osteoclast-like cells. The Figure illustrates the functional contribution of Runx2 to vascular calcification.

These findings confirm the important role of osteogenic differentiation of VSMCs in arterial calcification. They further demonstrate a major role of Runx2 not only in this process, but also in promoting macrophage infiltration into calcified atherosclerotic lesions and RANKL-mediated macrophage differentiation into osteoclast-like cells. The function of these cells found in the vicinity of calcified areas is not yet clear. From a clinical point of view, targeting Runx2 or Runx2-regulating signals in VSMCs may represent a novel strategy for prevention and therapy of vascular calcification.

Tilman B. Drüeke

Association of provider–patient visit frequency and patient outcomes on hemodialysis

Slinin *et al.*, *J Am Soc Nephrol* 2012; **23**: 1560–1567; doi:10.1681/ASN.2012010051

Hemodialysis mortality rates vary both within and between countries, and this disparity has led to speculation about whether different models of medical supervision and practice affect outcomes. Practices vary quite markedly, from very frequent medical review at each dialysis session to monthly or even less frequent review in the dialysis center, coupled with formal 6-month or annual clinic reviews. The proponents of more frequent review in the dialysis center have argued that greater doctor–patient contact could improve both dietary and medication compliance and limit intradialytic weight gains, with improved blood pressure and phosphate control. In the United States, the standard approach had been monthly review of all patients in dialysis centers, but the introduction of additional payments for more frequent medical review led many centers to increase to weekly medical review. Slinin and colleagues analyzed outcomes from patient data submitted to the US Renal Data System database, comparing cohorts of patients reviewed monthly or more frequently. Patients reviewed less frequently were more likely to be younger, Caucasoid, of lower socioeconomic status, and of rural residence, and, during the run-in pre-study period, more likely to miss dialysis sessions and less likely to have been hospitalized. More frequent review did not improve either raw or adjusted 1-year patient mortality. However, after adjustment, first and repeated admissions were marginally, but significantly, reduced with more frequent review. Although the differences were small, this finding would translate into considerable health-care cost savings.

Whether doctor–patient consultation duration and quality were similar with more frequent review is unknown, and similarly, surrogates of the quality of care delivered, such as dialysis attendance, intradialytic weight gains, blood pressure, and phosphate control, were not reported. However, since the change in reimbursement policy and more frequent medical review, the hospital admission rate of US dialysis patients has decreased.

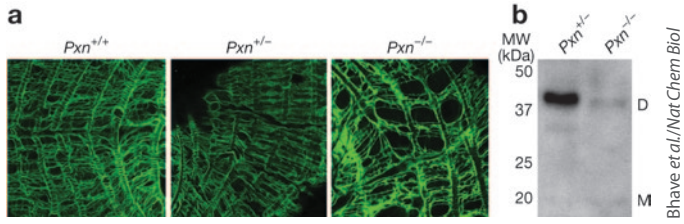
Andrew Davenport

Unraveling the chemistry of the glomerular basement membrane

Bhave *et al.*, *Nat Chem Biol* 2012; **8**: 784–790; doi:10.1038/nchembio.1038

The structure and function of type IV collagen within the glomerular basement membrane (GBM) are crucial to normal GBM function; thus, understanding how the component collagen strands are assembled is important for understanding glomerular function in health and disease. It has been known that type IV collagen is assembled from protomers. The binding of the C-terminals of the protomers occurs by intermolecular sulfilimine cross-links. Disruption of these sulfilimine bonds allows exposure of the collagen type IV epitopes to the immune system as the target autoantigens in Goodpasture's syndrome. Up until now, the molecular mechanism allowing these unusual chemical bonds to form has been unknown. Using a *Drosophila*-based system, Bhave *et al.* have identified an orphan enzyme, of previously unknown function, that is present in the GBM as the enzyme responsible for the formation of these bonds. The enzyme peroxidasin was originally identified as a basement membrane protein in *Drosophila* in 1994, but its function until now has been unknown. The investigators used a mouse endodermis cell line that produces small quantities of collagen IV and forms basement membrane *in vitro*. Using this cell culture system in the presence or absence of peroxidase inhibitors, Bhave and colleagues identified the existence of an endogenous peroxidase within the basement membrane that forms these sulfinimide bonds. This enzyme was subsequently shown to be peroxidasin, which is active under oxidative conditions. To confirm the role of this enzyme *in vivo*, *Drosophila* peroxidasin (Pxn) mutant larvae were generated, which show distorted collagen IV in the heterozygote ($Pxn^{+/-}$) and complete-knockout ($Pxn^{-/-}$) animals compared with wild type ($Pxn^{+/+}$) (Figure). Taken together, these novel findings on the chemistry of the GBM move us still closer to understanding normal GBM function and, potentially, how the Goodpasture antigen becomes exposed in disease.

P. Toby Coates



Peroxidasin is critical for collagen IV and basement membrane integrity. (**a**) Confocal fluorescence microscopy images of *Drosophila* anterior midgut using a collagen IV GFP protein trap line (*viking*^{G454}) to delineate collagen IV distribution. Representative sections from wild-type $Pxn^{+/+}$, heterozygote $Pxn^{+/-}$ ($Pxn^{+/f07229}$), and mutant $Pxn^{-/-}$ ($Pxn^{f07229/f07229}$) flies are shown. Distorted and torn collagen IV networks (arrows) with gross defects ('holes') in the circumferential muscle layer (asterisks) typified $Pxn^{-/-}$ sections. Scale bars, 10 μm. (**b**) Immunoblot of collagenase-solubilized basement membrane isolated from *Drosophila* $Pxn^{+/-}$ and $Pxn^{-/-}$ larvae.